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Navigating Asia Pacific Regulatory Challenges

Cathy Craft and Lorrie Piestrak

Siemens Healthcare Diagnostics Inc

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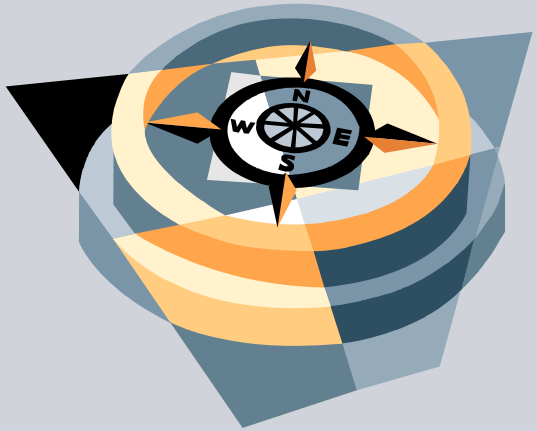

Navigating Asia Pacific Topics

- China
- Korea
- Japan
- Australia & New Zealand

China

Navigating Asia Pacific Regulatory Challenges —China

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- The State Food and Drug Administration (SFDA) is the National Competent Authority of the People's Republic of China.
- SFDA is part of the Ministry of Health and has regulatory and legal enforcement functions.
- SFDA is responsible for protecting the public health by assuring the safety, efficacy, and security of drugs, biological products, medical devices, food supply and cosmetics. IVD specific regulations include:
  - Order No. 16 – Provision of Medical Device Registration, 2004-8-16
  - Order No. [2007] 229 – Provision on *In Vitro* Diagnostics reagents' registration: 2007-06-01
  - Order No. [2007] 609 – Format and Basic Requirements of IVD reagents' registration submissions: 2007-09-03
  - Clinical Research for *In Vitro* Diagnostic Reagent Technical Guideline

IVD Product Classifications —China

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For the purpose of medical device administration, IVD products are divided in three categories with different registration requirements.

	Class I *Low risk*	**Class II** *Medium Risk*	**Class III** *High Risk*
Definition	▪ Microorganism culture medium (not used for micro-organism identification and medicine sensitivity experiment); ▪ Products for specimen treatment, e.g. hemolytic agents, diluents, staining solutions, etc.	▪ IVD products that do not fall in Class I or Class II are classified as Class II	▪ IVD related to the inspection of Antigen, antibody and nucleic acid etc. for pathogen; blood group and tissue typing, human genes, inherited diseases; narcotic, psychotropic and toxic drugs; target sites of curative drugs, tumor markers and allergies
Instruments [1)]	▪ Automation	▪ Clinical Chemistry ▪ Hematology ▪ Hemostasis ▪ Plasma Proteins ▪ POC testing (Urinalysis, Blood Gas, Diabetes, Cardiac)	▪ Immunoassay Microbiology ▪ Drug testing system
Reagents, Consumables, Accessories [2)]	▪ Sample treatment products: hemolytic agents diluents, staining solution ▪ Washing buffer, releasing agent	▪ Proteins, Glucose, Hormones, Enzymes, Esters, Vitamins, inorganic ions, TDM, auto-antibodies, microbiological identification and antimicrobial agent susceptibility and immunological tests	▪ Infectious diseases, Blood/tissue typing, Human genes, Hereditary diseases, Narcotics, drug of abuse and toxic drugs, Tumor markers, Allergens

1 Regulation: SFDA Order No. 16, introduced in 2000, revised in 2004
2 Regulation: SFDA Order No. 229, introduced in 2007

Challenge in Understanding Classification —China

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However, some IVDs are classified as pharmaceuticals & excluded from device registration:

- **IVDs intended to screen donor blood**
  - **A, B, O blood typing reagents**
  - **Hepatitis B Surface antigen ELISA Diagnostic Regent (HBsAG ELA)**
  - **Hepatitis C Surface Antigen ELISA Diagnostic Reagent (Anti-HCV ELA)**
  - **AIDS Virus Antibody ELISA Diagnostic Reagent (Anti-HIV ELA)**
  - **Syphilis Diagnostic Reagent (RPR & USR)**
- **IVDs containing radio-labeled components (RIA)**

The same analyte could be classified differently (device vs. pharmaceutical) based on the testing methodology.

Calibrators and controls may have different classifications than their corresponding assay

The IVD Registration Procedure Consists of 3 Steps: Documentation, Testing and Approval—China

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IVD Registration Procedure

Doc

- **Planning**
- **Collecting & Prepare Information**

Testing

- **Draft Product Standards**
- **Sample Collection**
- **Local Type Test (China)**
- **Local Clinical Trial (China)**

Approval

- **Submission of Dossier**
- **SFDA Technical Review (1)**
- **Collect Supplemental Information**
- **SFDA Technical Review (2)**
- **SFDA Technical Review (3,4, ...)**
- **Approval**

Description of Key Steps

Planning

- Establish a list of registration priorities

Documentation

- Compile application Dossier, include required documents & test results

Testing

- Draft product standard: compile product specifications in SFDA format
- Sample collection: collect samples of 3 different manufacturing lots
- Local Type Test: Complete Laboratory tests based on product standard, at an SFDA appointed & approved testing lab; tests may include mechanical, physical, electrical, safety, chemical & biocompatibility testing
- Local Clinical Trials: Required for Class II and III reagents, the trials must be performed in Provincial level hospitals.
  - Class II: 200 samples – 2 facilities
  - Class III: 1,000 samples – 3 facilities

Approval

- SFDA Technical Review: Provincial evaluation authorities review domestic Class I and II products. The State Evaluation Institutions review domestic Class III products and all classes of imported product
- Supplemental Information: If SFDA reviewer needs to clarify technical issues or finds the application incomplete, the applicant is requested to answer questions or submit additional data; this request occurs frequently

IVD – Registration Dossier (Final Submission) —China

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- Application Sheet
- Certifying Documents (Country of Origin Approval e.g. DOC, FDA; ISO certificate etc.) and Company Letters
- Product Summary
- IFU & Labels (English & Chinese)
- Product Standard
- Type Testing Final Report
- Raw Materials Specs, Acceptance Criteria & QC Testing
- Manufacturing Process—from Raw Materials—Intermediate-Finished Kit
- Performance Evaluation (In-House Testing): EU &/or USA
- Determination of Reference Interval
- Stability Study: Protocol
- Clinical Study: (a) Data in Original Country; (b) Data in China
- COA+ Batch Records (3 Consecutive Lots)
- Labeling Samples
- QS (Chinese) Audit Report (Invitation Letter)

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Notes on Clinical Trials—China

- Clinical trials are conducted in China to verify clinical characteristics of Class II & III IVD products vs. “on the market” devices
- For Class II Reagents:
  - Minimum of 2 hospitals should be selected as trial sites
  - Minimum of 200 samples (total) are required
- For Class III Reagents:
  - Minimum of 3 hospitals (in different cities) should be selected as trial sites
  - Minimum of 1,000 samples (total) are required
- Special sampling considerations:
  - Blood Screening: at least 10,000 subjects
  - PCR, RIA & Flow: at least 500 subjects
  - Narcotics, psychotropic drug detection: at least 500 subjects
- Clinical trial procedure can be conducted in parallel with Type-Testing
- Duration is typically 4 months to 2 years

Additional Information —China

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- China requires information that is not supplied to other countries (e.g., Batch Records)
- Documents from the Manufacturer must be translated into Chinese and notarized, adding cost and time
- Delays due to lack of precedent on interpretation of regulations by:
  - SFDA Reviewers
  - Industry
- Coordination and planning are essential for the Type Testing/Clinical Trials
  - Consider products having long expiration dating that are not manufactured frequently
- Ensure contracts with OEMs contain clauses to provide Batch Records

Additional Information —China

- *State Food and Drug Administration of the People's Republic of China*

  Website: *www.sfda.gov.cn*

- 96 New device standards—34 mandatory and 64 recommended go into effect June 1, 2012
  - Standards cover orthopedic transplant, dental, and sterile medical equipment packaging testing methods.

South Korea

Navigating Asia Pacific Regulatory Challenges —South Korea

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- Competent Authority: Korean Food and Drug Administration (KFDA)
- Certification Body:
  - Korean Testing Laboratory, Division of Korea Institute of Industrial Technology (KITECH-KTL)
  - Seoul Institute of Health and Environment (SIHE): Pharmaceuticals
- Relevant Regulations:
  - Medical Device Law: Medical Device
  - Pharmaceuticals Affairs Law: Pharmaceuticals

Current IVD Regulation —South Korea

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- IVD products are classified in two categories
  - Instrument
    - Class II: PCR – CFG, ISO, Operator Manuals, Technical File
    - Class I: CFG, ISO, Operator Manuals
  - Reagents
    - Pharmaceuticals (Manual Reagents): FSC, IFU, Technical File
    - Automatic Reagents: FSC, IFU

New IVD Regulation —South Korea

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- All IVD products classified into four classes
- Timeline for Implementation for currently marketed devices:
  - Class IV – Register by December 31, 2011
  - Class III – Register by December 31, 2012
  - Class I and II – Register by December 31, 2013

New IVD Regulation – Classification —South Korea

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- Class I – General purpose devices—examples:
  - General diagnostic instruments, dye reagents for cell and tissue
- Class II – Self-testing products, product which support non-critical medical decisions—examples:
  - Allergens, RF assays, urine strips, pregnancy tests for home use, Vitamin levels
- Class III – High risk devices impacting patient treatment, disease management—examples:
  - Infectious disease testing, fetal screening, coagulation testing, cardiac markers
- Class IV – Highest Risk—examples:
  - Blood screening, organ transplant screening, blood grouping, high-risk viruses

Class IV High-Risk Requirements —South Korea

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- A market approval from KFDA consists of a technical file review and type testing
- Technical File includes:
  - Components and Composition
  - Product Specifications and Appearance
  - Manufacturing Methods
  - Test Reports for 3 Sequential Lots/Testing SOPs
  - IFU, User, Installation and Service Manual
  - Development background, measuring principles and parameter selection
  - Clinical Studies & Performance Testing
    - Clinical Sensitivity, Analytical Sensitivity, Measuring Range, Cut-Off, Method Comparison (approved predicate), Reproducibility, etc.
- ISO 13485 & Free Sales Certificate

Class IV High-Risk Requirements —South Korea (concluded)

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- Additional Testing/Requirements:
  - QC Release records for each lot
  - Local QC final release testing (Korea)
  - Manufacturing Site Audit
- Time to Approval: 2 Months to 1 Year

Japan

Navigating Asia Pacific Regulatory Challenges —Japan

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- The Ministry of Health, Labor and Welfare (MHLW) is the National Competent Authority for Japan
- The Pharmaceutical and Medical Devices Agency (PMDA)—an affiliate body of MHLW established on April 1, 2004; who performs the following:
  - Health Damage Relief Activities
  - Reviews Product Registration Documentation
  - Countermeasure Activities for Safety After Product Launch
- (Revised) Pharmaceutical Affairs Law (PAL) effective April 1, 2005
  - PAL Enforcement Ordinance
  - PAL Implementation Regulations
  - Notification is from Director-General and heads of WHO Evaluation and Licensing Division

Navigating Asia Pacific Regulatory Challenges —Japan

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Marketing Authorization Holder (MAH): The person who has obtained the license for the marketing business from the Minister and is responsible for all products marketed in Japan. The MAH must:

- Have an agreement with the manufacturer based on GQP ordinance ("Addendum Concerning Manufacturing and Quality Control of *In Vitro* Diagnostics and Medical Device to Distributorship Agreement of December 2004"
- Take appropriate action according to local regulations in event of a Field Correction/Recall
- Display MAH license in prominent location (hung on wall in entryway)

IVD Product Classifications —Japan

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For the purpose of medical device administration, IVD products are divided in three categories with different registration requirements.

IVD Instruments:

- Class I—a sub-category of medical instruments considered as low risk products. Requires PMDA notification (not approval or third party certification)

Reagents:

- Class I—Analytes with calibrators which can be traced to reference materials defined by MHLW in Notice No. 20, 2005, 3, 29
  - Considered low risk
  - Registered by submitting notification to PMDA, (no data included)
- Class II—Analytes currently on Japan market and not classified as I or III
  - Considered moderate risk by MHLW
  - Registration documents submitted to a Third Party, who issues a certificate
- Class III—New analytes not currently on Japan market
  - Also those considered high risk (life sustaining, infectious disease, human genomes, tumor markers, bacterial identification, etc.)
  - Registration documents submitted to PMDA, MHLW issues certificate

Class I Submission—Japan

Also needed for all reagent classes:

- Product Name & Classification
- Intended Use
- Shape, Structure (Tablets, Liquid) and Principle
- Active Ingredients (Substances Involved in Reaction)
- Specifications for Sensitivity, Specificity, Reproducibility
- General Method Overview
- Manufacturing Information/Flowchart
- Storage and Shelf Life
- Manufacturing Site
- Miscellaneous Information, Production & Sales License Holders, Accessories, IFU, etc.

Calibrator must be traceable to standards or reference materials listed by MHLW. If not, provide traceability process and justification.

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Class II Submission—Japan

All Class I Elements, and:

- Product History, background and marketing information
  - List of countries where sold,
- Product Performance Specifications
  - Data for 3 lots—sensitivity, specificity, reproducibility
  - Assay range information (Minimum detection limit)
  - Information on calibrator reference materials
  - Explanation of conformity to the essential requirements (IVDD Annex I, DOC)
- Stability Information
  - Data for 3 lots—shelf life +1 month
- Product Performance Attributes
  - Materials of performance—recover testing, linearity data
  - Materials of procedure—reaction conditions, special precautions
  - Specimen requirements
  - Method comparison (n ≥50) on two predicates
- Risk Analysis

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Class III Submission—Japan

All Class I and Class II elements, and:

- Method comparison difference from Class II
  - n ≥100 on two predicates
- Clinical Trial Data
  - Data for minimum of 150 specimens tested at minimum of 2 clinical sites (one must be in Japan)
  - Data from outside Japan may be acceptable; discuss w/MHLW prior to submission
  - Specimen attributes: Age, Sex, Race, Illness, Drugs, etc.

Predicate Devices: Additional Information —Japan

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Predicate Devices:

- Must be approved or certified in Japan
- Must be commonly used in clinical applications
- Must have good performance
- If multiple operating principles (technologies) in Japan, select 2 different technologies
- If standard methods or test methods recommended by a public organization (e.g., WHO), a standards organization (NCCLS, JCCLS, etc.) these may be used

Additional Information —Japan

- *The Ministry of Health, Labor and Welfare (MHLW)*
  1-2-2 Kasumingaseki
  Chiyoda-Ku, Tokyo, 100-8916, Japan

  Website: www.pmda.go.jp (Look for English Box)

Australia & New Zealand

Overview
—Australia & New Zealand

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- Regulatory Authority:
  - Australia – Australian Register of Therapeutic Goods (ARTG)
    Therapeutic Goods Administration (TGA); conformity assessment branch
  - New Zealand* – MEDSAFE
- Regulation:
  - Australia - Therapeutic Goods Act of 1989/2002
  - New Zealand* – NZ Medicines and Medical Devices Act
- Classification – Four levels, risk based
- Standards – Allowable with presumption of conformity but not mandatory

* New Zealand does not currently have detailed MD regulations; TransTasman harmonization has not yet occurred.

Definitions of Medical Device —Australia

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"any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for one or more of the following:

(i) diagnosis, prevention, monitoring, treatment, alleviation of disease

(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;

(iii) investigation, replacement or modification of the anatomy or of a physiological process;

(iv) control of conception"

Classification —Australia

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IVD Classification is based on manufacturers intended use, level of risk posed through use

- Class IV – High public health risk—IVDs used to screen for transmissible agents in blood, tissue, organs and related products for transfusion/transplantation, or to detect the presence of or exposure to a serious disease with a high risk of propagation—examples
  - HIV, HCV, HBV, HTLV, SARS, Smallpox
- Class III – Used for detection of biological markers to assess immunological compatibility for transfusion or transplant, detection of transmissible agents posing a moderate public health risk—examples
  - Self-testing: blood glucose monitoring, genetic testing, infectious disease screening, maternal screening

Classification —Australia (concluded)

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IVD Classification is based on manufacturers intended use, level of risk posed through use

- Class II – Low public health risk—largest segment of commercially available IVDs—examples
  - Non-assay specific QC materials, urine dipsticks, liver enzymes
- Class I – No public health risk—examples
  - IVD instruments, culture media, specimen receptacles

Risk-Based Regulation —Australia

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All manufacturers and sponsors must have post-market surveillance and adverse event reporting procedures

Class 1

- **DOC**
- Elements of a QMS, QMS not assessed
- Must hold technical documentation

Class 2

- **DOC**
- **Evidence of appropriate QMS**
- Must hold technical documentation

Class 3

- **DOC**
- **Submission of Technical File for subset of Class 3 IVDs (e.g., home-use)**
- **Evidence of appropriate QMS**
- Must hold technical documentation

Class 4

- **DOC**
- **Examination of Design Dossier with emphasis on:**
  - **Performance Testing**
  - **Compliance with EPs**
  - **Risk Analysis**
- **Evidence of appropriate QMS**

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Additional information: Essential requirements Checklist, Guidance Documents on Classification, Fees and Inclusion into the TGA registry can be found here –

http://www.tga.gov.au/ivd/ivd-guidance.htm

Reflections

Reflections on Product Registrations in Asia Pacific